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10/719,553	11/20/2003	Hans Henrik Ipsen	04305/100E144-US2	3430

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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/719,553	IPSEN ET AL.	
	Examiner	Art Unit	
	NORA M. ROONEY	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *36-96* is/are pending in the application.

4a) Of the above claim(s) *44-65 and 74-96* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *36-43 and 66-73* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 04/30/2008 has been entered.

2. Claims 36- 96 are pending.

3. Claims 44-65 and 74-96 stand withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention.

4. Claims 36-43 and 66-73 are currently under examination as they read upon a recombinant mutant Bet v 1 allergen and the 'Triple-patch' mutant of species of 'ix.' in claim 37.

Double Patenting

5. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined

application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

6. Claims 36-43 and 66-73 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-22, 25-26, 28, 35, 37-39, 64 and 66-85 of copending Application No. 10/001,245. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims arrive at similar allergenic variants, and by what appears to the Examiner to be the same method of selection, or if not, by an obvious variant thereof. Specifically, Claims 1-22, 25-26, 28, 35, 37-39, 64 and 66-85 teach a mutant Bet V1 allergen with 1 or more substitutions, wherein said substitutions occur at many amino acid residues that are identical positions between the '245

application and the instant application, such as those recited in copending claim 22 and instant claim 37. Claim 22 of the '245 application recites substituting unspecified amino acids at one or more given positions, whereas the instant application recites specific substitutions at some of the same positions. However, on page 29 of the '245 specification in example 2595, the identical 'triple patch' mutant species of instant claim 37 is disclosed. Therefore, the claims are not patentably distinct from one another for the same reasons as set forth in the Office Action mailed on 10/31/2007.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicant's arguments submitted on 04/30/2008 have been fully considered, but are not found persuasive.

Applicants argue:

> "Applicants confirm that the aforementioned co-pending application has not issued as a patent. Accordingly, Applicants are not required to respond to the rejection at this time."

It is the Examiner's position that the rejection stands until the rejected claims are cancelled or until a terminal disclaimer is filed.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 36, 38-43 and 66-73 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

Applicant is in possession of a recombinant mutant allergen from birch pollen major allergen Bet v a of SEQ ID NO:37 having the amino acid substitutions recited in claim 37.

However, applicant is not in possession of: a recombinant mutant Bet v 1 allergen derived from a naturally-occurring Bet v 1 allergen from the order Fagales, said recombinant mutant Bet v 1 allergen having: (a) a substitution of **a solvent-accessible amino acid residue that is conserved among Bet v 1 homologous allergens within the order Fagales**, said substitution occurring in **a B-cell epitope of said naturally-occurring Bet v 1 allergen**; (b) reduced specific IgE binding compared to said naturally-occurring Bet v 1 allergen from which it is derived; and (c) **an α-carbon backbone tertiary structure that is preserved as compared to the α-carbon backbone tertiary structure of said naturally-occurring Bet v 1 allergen** of claim 36; wherein said **solvent accessible conserved amino acid residue has a solvent accessibility of at least 20%** of claim 38; wherein **said conserved solvent-accessible amino acid residue is conserved with more than 70% identity among Bet v 1 homologous allergens within the taxonomic order from which said naturally-occurring Bet v 1 allergen originates**

of claim 39; wherein the specific IgE binding of said mutant Bet v 1 allergen compared to said naturally-occurring Bet v 1 allergen from which it is derived is reduced by at least 5% of claim 40; wherein **the average root mean square deviation of the atomic coordinates comparing the α-carbon backbone tertiary structures of said recombinant mutant Bet v 1 allergen and said naturally-occurring Bet v 1 allergens is less than 2 Å** in claim 41; wherein **said conserved solvent-accessible amino acid residue is within a patch of conserved amino acid residues connected over at least 400 Å of the surface of said naturally-occurring Bet v 1 allergen**; wherein said **solvent-accessible amino acid residue that is conserved among Bet v 1 homologous allergens within the taxonomic order from which said naturally-occurring Bet v 1 allergen is substituted with an amino acid that is not conserved among Bet v 1 homologous allergens within the taxonomic order from which said naturally occurring Bet v 1 allergen occurs**; or a recombinant mutant allergen derived from a naturally-occurring allergen within the order Fagales that is **homologous to Bet v 1 allergen**, said recombinant mutant allergens having: (a) **a substitution of a solvent-accessible amino acid residue that is covered among homologous allergens within the taxonomic order Fagales**, said **substitution occurring in a B-cell epitope of said naturally-occurring allergen**; (b) reduced specific IgE binding compared to said naturally-occurring allergen; and (c) **an α-carbon backbone tertiary structure that is preserved as compared to the α-carbon backbone tertiary structure of said naturally-occurring allergen** of claim 66; wherein said allergens homologous to Bet v 1 have an amino sequence that yields a BLAST probability of less than .1 when compared to an amino acid sequence of SEQ ID NO:37 of claim 67; wherein **said solvent-accessible conserved amino acid residue has a solvent accessibility of at least 20%** of claim 68; wherein **said conserved**

solvent-accessible amino acid residue is conserved with more than 70% identity among homologous allergens within the taxonomic order from which said naturally-occurring allergen originates of claim 69; wherein the specific IgE binding of said mutant allergen compared to said naturally occurring allergen from which it is derived is reduced by at least 5% of claim 70; wherein **the average root mean square deviation of the atomic coordinates comparing the α-carbon backbone tertiary structures of said recombinant mutant allergens and said naturally-occurring allergen is less than 2 Å** of claim 71; wherein **said conserved solvent-accessible amino acid residue is within a patch of conserved amino acid residues connected over at least 400 Å^2 of the surface of said naturally-occurring allergen** of claim 72; or wherein **said solvent-accessible amino acid residue that is conserved among homologous allergens within the taxonomic order from which said naturally-occurring allergen occurs** for the same reasons as set forth in the Office Action mailed on 10/31/2007.

Applicant's arguments submitted on 04/30/2008 have been fully considered, but are not found persuasive.

Applicant argues:

> "Focusing first on claim 36, consideration of these factors establishes that the Applicants were in possession of the claimed invention when the application was filed, as follows.
>
> Claim 36 is directed to a genus of recombinant *Bet v 1* allergens derived from a naturally-occurring *Bet v 1* allergen from the order *Fagales* that have (a) a substitution of a solvent-accessible amino acid residue that is conserved among *Bet v 1* homologous allergens within the order *Fagales*, said substitution occurring in a B-cell epitope of the naturally-occurring *Bet v 1* allergen; (b) reduced specific IgE binding compared to the naturally-occurring *Bet v 1* allergen from which the mutant allergen is derived; and (c) an α-carbon backbone tertiary structure that is preserved as compared to the α-carbon backbone tertiary structure of the naturally-occurring *Bet v 1* allergen.

1. Actual reduction to practice. The instant application discloses and characterizes three independent recombinant mutant *Bet v 1*, the single point mutants, Glu45Ser and Pro108Gly, and the double point mutant, Asn28Thr + Lys32Gln, and a fourth recombinant mutant *Bet v 1* bearing the combination of each of the aforementioned four point mutations, the so-called "triple patch mutant," Glu45Ser, Asn28Thr + Lys32Gln, Pro108Gly. Each of the disclosed and characterized recombinant *Bet v 1* allergens had the properties of the claimed allergens, i.e., they reduced IgE binding and retained a preserved α-carbon backbone compared to native allergen. Thus, the application discloses four examples in which the genus of claim 36 was reduced to practice. In addition, the application discloses that point mutations Thr10Pro, Asp25Gly, Asn47Ser, Lys55Asn and Thr77Ala are incorporated into recombinant mutant *Bet v 1* mutant allergens.

2. Disclosure of drawings or structural chemical formulas. The application sets forth the sequence of *Bet v 1* in Fig. 3, along with the precise position of the aforementioned mutations. Thus, the application discloses the structural formula of the exemplified mutants.

3. Identifying characteristics.

(i) Complete structure. The Application sets forth the complete structure of the exemplified mutants.

(ii) Partial structure. Each of the recombinant mutants of claim 36 is derived from the *Bet v 1* sequence set forth in Fig. 3. Thus, the application includes a partial sequence for each of the recombinant *Bet v 1* allergens of claim 36.

(iii) Physical and/or chemical properties. The genus of allergens encompassed by claim 36 are substitutions of amino acids that are conserved among *Bet v 1* homologous allergens within the order *Fagales,* said substitution occurring in a B-cell epitope of said naturally-occurring *Bet v 1* allergen. Moreover, the pre-existing general knowledge in the art supplements the description: One of ordinary skill in the art the art would thus readily understand that "substitution" refers to the replacement of a *Bet v 1* amino acid with another of the other 19 amino acids. The application further sets out that amino acids to be substituted are located on the surface. Such amino acids have a solvent accessibility (water) of at least 20%, preferably 20-80% and more preferably 30-80%. *See* specification at page 19, lines 30-35. A further preference is the substitution of a polar residue for another polar residue and a non-polar residue for another non- polar residue. The amino acid to be substituted is further identified as a "residue that is conserved among *Bet v 1* homologous allergens within the order *Fagales." See* claim 36. The specification sets forth that "major birch pollen allergen *Bet v 1* shows about 90% amino acid sequence identity with major allergens from pollens of taxonomically related trees, i.e., *Fagales."* Specification at page 22, line 36 through page 23, line 2. *Bet v 1* proteins are even more highly identical to each other than allergens from taxonomically related trees, e.g. 95-100% identity. Using standard sequence alignment programs available at the time the application was filed, one of ordinary skill in the art could readily align and identity conserved amino acids among the *Bet v 1* allergens from the order *Fagales. See,* e.g., specification at page 24, line 23, et seq., section entitled "Sequence Alignment." Thus, the specification provides certain chemical and physical properties for the substituted amino acids of claim 36. Moreover, the pre-existing general knowledge in the art supplements the description: by the time the application was filed, the three dimensional structure of *Bet v i* protein had been determined and published. *See* reference to Ghajhede et al., 1996, *Nature Structural Biol.* 3:1040-1045 at page 23, line 25 of the specification. Knowledge of the three dimensional structure allows identification of solvent accessible amino acids. The high level of identity means that using the knowledge of the three dimensional structure of even one *Bet v 1* protein of to identify solvent accessible amino acids and alignment procedures allows identification of the solvent accessible amino acids of any *Bet v i* allergen from the order *Fagales.* Lastly, recombinant mutant *Bet v i* allergen of claim 36 has "an (x-carbon backbone tertiary structure that is preserved as compared to the (x-carbon backbone tertiary structure of said naturally-occurring *Bet v* i allergen," i.e., the recombinant Bet 1 has a native conformation. At the time the application was

filed, it was generally known in the art was that replacement of surface amino acids would have a reduced probability of disrupting three dimensional structure. The specification sets out explicitly that amino acid residues having a solvent exposure of less than 20% were "not regarded as relevant for mutagenesis due to the possible disruption of structure." Specification at page 24, lines 17-19. Thus, the specification and the general knowledge in the art provides guidance on the chemical and physical nature of the substitutions to be made in the recombinant allergens of claim 36.

(iv) Functional characteristics coupled with a known or disclosed correlation between function and structure. The mutant *Bet v i* allergens of claim 38 have the property of reduced IgE binding compared to the allergen from which they are derived. As set forth in the "Background of the Invention," it was general knowledge in the art at the time the application was filed that allergens with reduced IgE binding could be produced by site-directed mutagenesis. See specification and cited references at page 7, line 15, et seq. The specification further discloses that the amino acids available for antibody binding are located on the surface of allergens (see specification at page 19, lines 30-32) and that dominant IgE epitopes, in particular, are typically contained within conserved patches on the surface of allergens *(see* specification at, e.g., page 20, lines 4-13 and page 23, lines 24-36). Thus, the functional characteristic of reduced IgE binding flows directly from (i.e., is "coupled with") the known property of IgE epitopes to be present on the surface of allergens, particularly in conserved patches on the allergen surface, and the disclosed and well known correlation that disrupting IgE epitopes will reduce IgE binding.

d. Method of making the invention. As discussed in Applicants' previous response filed on August 8, 2007, the specification discloses methods for making the claimed invention. Thus, the specification gives extensive guidance that allows one of ordinary skill in the art to determine which conserved amino acids of a *Bet v 1* allergen from the taxonomic order *Fagales* should be substituted such that the recombinant mutant allergen would have the claimed properties of retaining native structure and exhibiting reduced IgE binding. It is noted that following Applicants' previous response, the Examiner withdraw a prior rejection of the claims for lack of enablement. It is respectfully submitted that withdrawal of the enablement rejection is an acknowledgment that the specification discloses a method of making the invention. It is noted, moreover, although the enablement and written description requirements of section 112, are independent requirements, the Federal Circuit has stated:

Those two requirements usually rise and fall together. That is, a recitation of how to make and use the invention across the full breadth of the claim is ordinarily sufficient to demonstrate the inventor possesses the full scope of the invention, and vice versa.

Lizardtech, Inc. v Regents of the University of California, 424 F.3d 1336,1345 (Fed. Cir. 2005). *See also Capon v. Eshhar,* 418 F.3d 1349, 1360 (Fed. Cir. 2005) (Although separate requirements, the "legal criteria of enablement and written description are related and often met by the same disclosure.")

e. Level of skill and knowledge in the art. The consideration of the factors set out above demonstrates that the level of skill and knowledge in the art related to *Bet v i* allergens from the order *Fagles* and IgE epitopes was high. Thus, the state of the was such that it was known, for example, that *Bet v i* allergens include dominant IgE epitopes and that they reside in surface patches, that *Bet v i* proteins from the order *Fagales* share a high level of identity and exhibit cross reactivity, and that substitution of amino acids on the surface of *Bet v i* allergens could disrupt IgE epitopes and lower IgE binding.

f. Predictability in the art. Each of the working examples set forth in the specification has the properties called for in claim 36. Moreover, the specification includes the results for all of the mutants that had been made at the time the application was filed. Thus, it is apparent that the claimed mutant allergens may be predictably derived using the methods set forth in the application.

In summary with respect to claim 36, the specification discloses *Bet v 1* mutant allergens with the properties set forth in claim 36, provides a partial sequence for each of the claimed mutant allergens in that

they are each derived of *Bet v 1* allergens from the order *Fagales,* and provides detailed guidance on the nature of the substitutions to be made in the claimed allergens and the functional characteristics exhibited by the claimed allergen. Moreover, the skill and knowledge in art is high. For at least these reasons, one of ordinary skill in the art would recognize that the inventors were in possession of the genus of claim 36.

The specification similarly provides written description for the other claims:

Claim 66 differs from claim 36 in that it is directed to a recombinant mutant allergen derived from a naturally-occurring allergen within the order *Fagales* that is homologous to *Bet v 1.*

The specification sets forth that:

The major birch pollen allergen *Bet v 1* shows about 90% amino acid sequence identity with major allergens from pollens of taxonomically related trees, i.e. *Fagales* (or instance hazel and hornbeam) and birch pollen allergic patients often show clinical symptoms of allergic cross-reactivity towards these *Bet v 1* homologous proteins.

Specification at page 22, line 36 through page 23, line 6. Based on the level of skill in the art at the time the application was filed, a worker of ordinary skill in the art would have recognized that the high degree of identity among *Bet v 1* homologous proteins from the order *Fagales* and the finding that birch pollen allergic patients exhibited symptoms of allergic cross- reactivity towards these homologous proteins indicates that *Bet v 1* homologous proteins from the order *Fagales* have highly similar primary sequences and three-dimensional structures~ indicating that the features that are set forth above and which indicate that the Applicants had possession of the mutant allergens for *Bet v 1* proteins from the order *Fagales* also hold for the broader genus of recombinant mutant allergens of *Bet v i* homologous proteins from the order *Fagales.* Thus, the specification provides written description for claim 66 for the same reasons it provides written description for claim 36.

The specification also provides written description for the mutant allergens of claims 38-43 and 67-72, which claims depend from claims 36 and 66, respectively. Thus, the general level of skill and knowledge in the art would readily allow one of ordinary skill in the art to use the known crystal structure of *Bet v 1* and/or sequence alignment of *Bet v 1* sequences to identify amino acids that have a solvent accessibility of 20% (claims 38 and 68), are conserved with 70% identity among *Bet v 1* allergens from the order *Fagales* (claims 39 and 69), wherein said conserved solvent- accessible amino acid residue is within a patch of conserved amino acid residues connected over at least 400A of the surface of said naturally-occurring *Bet v 1* allergen (claims 42 and 72), wherein the solvent-accessible amino acid residue that is conserved among *Bet v 1* homologous allergens within the taxonomic order from which said naturally-occurring *Bet v 1* allergen is substituted with an amino acid that is not conserved among *Bet v 1* homologous allergens within the taxonomic order from which said naturally-occurring *Bet v 1* allergen occurs (claims 43 and 73) and wherein said allergens homologous to *Bet v 1* have an amino sequence that yields a BLAST probability of less than 0.1 when compared to an amino acid sequence of SEQ ID NO: 37 (claim 67). The specification further provides extensive guidance on tests that can be used to determine with recombinant *Bet v 1* allergens have IgE binding reduced by at least 5%, compared to the naturally occurring *Bet v 1* allergen from which it is derived (claims 40 and 70) and wherein average root mean square deviation of the atomic coordinates comparing the a-carbon backbone tertiary structures of said recombinant mutant *Bet v 1* allergen and said naturally-occurring *Bet v 1* allergen is less than 2A (claims 41 and 71). Thus, the Applicants were also in possession of the subject matter of claims 38-43 and 67-72. "

The Examiner is aware of the changes to the guidelines for written description cite by Applicant. However, it remains the Examiner's position that the specification does not disclose a correlation between structure of the allergen and function (reduced specific IgE binding) and in this case functional limitations ("occurring in a B-cell epitope" and "α-carbon backbone tertiary structure that is preserved" of claim 36 "wherein said solvent accessible conserved amino acid residue has a solvent accessibility of at least 20%" of claim 38; "wherein the specific IgE binding of said mutant Bet v 1 allergen compared to said naturally-occurring Bet v 1 allergen from which it is derived is reduced by at least 5%" of claim 40; "wherein the average root mean square deviation of the atomic coordinates comparing the α-carbon backbone tertiary structures of said recombinant mutant Bet v 1 allergen and said naturally-occurring Bet v 1 allergens is less than 2 Å" in claim 41; "wherein said conserved solvent-accessible amino acid residue is within a patch of conserved amino acid residues connected over at least 400 Å of the surface of said naturally-occurring Bet v 1 allergen" of claim 42; "an amino sequence that yields a BLAST probability of less than .1 when compared to an amino acid sequence of SEQ ID NO:37" of claim 67; "wherein said solvent-accessible conserved amino acid residue has a solvent accessibility of at least 20%" of claim 68; "wherein the specific IgE binding of said mutant allergen compared to said naturally occurring allergen from which it is derived is reduced by at least 5%" of claim 70; "wherein the average root mean square deviation of the atomic coordinates comparing the α-carbon backbone tertiary structures of said recombinant mutant allergens and said naturally-occurring allergen is less than 2 Å" of claim 71; "wherein said conserved solvent-accessible amino acid residue is within a patch of conserved amino acid residues connected over at least 400 $Å^2$ of the surface of said naturally-occurring allergen" of claim 72) such that a skilled artisan would have known

what modification to make to the Bet v 1 allergens to attain the claimed function and functional limitations. "Possession may not be shown by merely describing how to obtain possession of member of the claimed genus or how to identify their common structural features" In re Kubin, of record, at page 16. In this instant case Applicants have not provided sufficient guidance as to what mutation or combination of mutations will result in the claimed functions and functional limitations. "Without a correlation between structure and function, the claim does little more than define the claimed invention by function" *supra*, at page 17.

Applicant's argument that the claims are adequatley edescribed because the specification has reduced to practice four mutants including two single point mutants, a double point mutant, and a "triple patch mutant," with reduced IgE binding and retained a preserved α-carbon backbone compared to native allergen is unpersuasive because these mutants are insufficient to describe the genus of all mutants that are encompassed by the instant claim recitations. There is also no indication in the specification as to how the particular point mutation strategy relates to the claimed functions such that one would know how to change the function by a particular mutation. The Examiner agrees that the specification discloses the complete structure of the exemplified mutants, however the structure of the genus of the recited mutants has not been adequately described. The Examiner does not agree that the state of the art at the time of invention as a supplement to the specification would adequately describe what mutants are encompassed by the instant claim recitations, given the known surface-exposed amino acids with solvent accessibility. The Examiner agrees that the claims are enabled in that one figure out what allergen mutants are encompassed by the instant claim recitation and make them.

However, the allergen mutants encompassed by the instant claim recitations with the recited functions and functional characteristics have not been described. The Examiner also maintains that mutants with homology to Bet v I with the claimed functions have also not been adequately described for the same reason.

The specification must adequately describe the structural features that allow one of ordinary skill in the art to produce Bet v 1 mutants substitutions occurring in a B-cell epitope and have α-carbon backbone tertiary structure that is preserved in addition to "wherein said solvent accessible conserved amino acid residue has a solvent accessibility of at least 20%" of claim 38; "wherein the specific IgE binding of said mutant Bet v 1 allergen compared to said naturally-occurring Bet v 1 allergen from which it is derived is reduced by at least 5%" of claim 40; "wherein the average root mean square deviation of the atomic coordinates comparing the α-carbon backbone tertiary structures of said recombinant mutant Bet v 1 allergen and said naturally-occurring Bet v 1 allergens is less than 2 Å" in claim 41; "wherein said conserved solvent-accessible amino acid residue is within a patch of conserved amino acid residues connected over at least 400 Å of the surface of said naturally-occurring Bet v 1 allergen" of claim 42; "an amino sequence that yields a BLAST probability of less than .1 when compared to an amino acid sequence of SEQ ID NO:37" of claim 67; "wherein said solvent-accessible conserved amino acid residue has a solvent accessibility of at least 20%" of claim 68; "wherein the specific IgE binding of said mutant allergen compared to said naturally occurring allergen from which it is derived is reduced by at least 5%" of claim 70; "wherein the average root mean square deviation of the atomic coordinates comparing the α-carbon backbone tertiary structures

of said recombinant mutant allergens and said naturally-occurring allergen is less than 2 Å" of claim 71; "wherein said conserved solvent-accessible amino acid residue is within a patch of conserved amino acid residues connected over at least 400 $Å^2$ of the surface of said naturally-occurring allergen" of claim 72. The instant applications identifies amino acid substitutions in *Bet v 1* (SEQ ID NO: 37) (Thrl0Pro, Asp25Gly, Asn28Thr, Lys32Gln, Glu45Ser, Asn47Ser, Lys55Asn, Thr77Ala, Prol08Gly) that may be used to make recombinant mutant allergens with single mutations or multiple mutations (Asn28Thr + Lys32Gln and "triple patch" mutant Glu45Ser, Asn28Thr + Lys32Gln, Prol08Gly) in which a conserved, solvent accessible amino acid in *Bet v 1* is substituted such that the mutant recombinant allergen derived thereby exhibits reduced IgE binding and retains the native ct-carbon backbone structure of *Bet v 1*. Moreover, each of the mutants tested (Glu45Ser; Prol08Gly; Asn28Thr + Lys32Gln; Glu45Ser, Asn28Thr + Lys32Gln, Pro 108Gly) had the properties called for in the instant claims, but there is no guidance on other mutant Bet v 1 allergens with these properties. The working examples for recombinant *Bet v 1* allergens with mutations in conserved, solvent accessible amino acids in patches on the surface of *Bet v 1* with reduced IgE binding and which retain a native α-carbon backbone structure are not sufficient support for the genes of all recombinant mutant Bet v 1 allergens encompassed by the claimed invention. In the instant case, definition by function does not suffice to define the genus because it is only an indication of what the allergen does and what functional properties it has, rather than what it is. Further, the ability to determine which mutants are encompassed by the claimed invention is not sufficient to describe the genus.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nora M. Rooney whose telephone number is (571) 272-9937. The examiner can normally be reached Monday through Friday from 8:30 am to 5:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen O'Hara can be reached on (571) 272-0878. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

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